PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	29 AUG 2005
Applicant's or agent's file reference 002441.00092 PP19817	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US04/25914	12 August 2004 (12.08.2004)	13 August 2003 (13.08.2003)

International Patent Classification (IPC) or both national classification and IPC

IPC(7): C12N 15/11, 15/85, 15/86; A61K 35/00, 48/00 and US Cl.: 536/23.1; 424/93.1; 435/325

Applicant

CHIRON CORPORATION

1. This opinion contains indications relating to the following items:

- ☒ Box No. I — Basis of the opinion
- ☐ Box No. II — Priority
- ☐ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV — Lack of unity of invention
- ☒ Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI — Certain documents cited
- ☐ Box No. VII — Certain defects in the international application
- ☐ Box No. VIII — Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(*b*) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Ram Shukla Telephone No. (571) 272-0735

Form PCT/ISA/237 (cover sheet) (January 2004)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/25914

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ in written format

☐ in computer readable form

c. time of filing/furnishing

☐ contained in international application as filed.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/25914

Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 2-4,9-11,18-22	YES
	Claims 1,5-8,12-17	NO
Inventive step (IS)	Claims 22	YES
	Claims 1-21	NO
Industrial applicability (IA)	Claims 1-22	YES
	Claims NONE	NO

2. Citations and explanations:

Claims 1,5-8,12-17 lack novelty under PCT Article 33(2) as being anticipated by KOJIMA et al. Granulocyte-Macrophage Colony-Stimulating Factor Gene-Transduced Tumor Cells Combined with Tumor-Derived gp96 Inhibit Tumor Growth in Mice. Human Gene Therapy. May 2003 Vol. 14, pages 715-728.

KOJIMA et al. provides guidance on a method of vaccination comprising the administration of a LLC lung cancer cell line stably transfected with a GM-CSF gene (Abstract; pg. 716, Material and Methods). Where the cell is inactivated by gamma-ray irradiation and suspended in PBS prior to administration to a C57BL/6 mouse. (Abstract; pg. 716, Material and Methods). Thus, by teaching all the limitations of the claims as written, KOJIMA et al. anticipates the instant invention as claimed.

Claims 2-4,9-11, and 18-21 lack an inventive step under PCT Article 33(3) as being obvious over KOJIMA et al. Granulocyte-Macrophage Colony-Stimulating Factor Gene-Transduced Tumor Cells Combined with Tumor-Derived gp96 Inhibit Tumor Growth in Mice. Human Gene Therapy. May 2003 Vol. 14, pages 715-728. in view of ZHAN et al. Control of IL-12 and IFN-gamma production in response to live or dead bacteria by TNF and other factors. Journal of Immunology. 1998. vol. 161, pages 1447-1453.

KOJIMA et al. provides guidance on the administration of a LLC lung cancer cell line stably transfected with a GM-CSF gene (Abstract; pg. 716, Material and Methods). Where the cell is inactivated by irradiation and suspended in PBS prior to administration to a C57BL/6 mouse. (Abstract; pg. 716, Material and Methods).

ZHAN et al. supplements the guidance of KOJIMA et al by teaching a method of vaccination comprising the heat inactivation of bacteria prior to their suspension in normal saline and administration to a mouse.

Based on the guidance provided by ZHAN et al. it would have been obvious to the person of ordinary skill in the art at the time the invention was made to inactivate the tumor cells of KOJIMA et al. by heat inactivation, or any other method commonly used in the art, such as ultra-violet light, or hydrogen peroxide.

The practitioner would be motivated to use methods of inactivation other irradiation because of the inherent danger of gamma-ray irradiation and the expense associated with maintaining a gamma-ray source.

The person of ordinary skill in the art would have a reasonable expectation of success because the use of alternative methods of cell inactivation would have been common practice in the art at the time of filing.

Claim 22 meets the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the detoxification of a host cell by genetic manipulation of the host cell's LPS genes.

Claims 1-21 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.